Editorial

The Ethics of Research in Children

The ethics of research in India has recently come under the scanner(1,2) raising the specter of demonizing all research. Increasingly, there is a fear among lay people that patients may be used as "guinea pigs". Three factors may have contributed to this murkiness:

- the "publish or perish" phenomenon, wherein researchers are pressurized to conduct research for professional advancement,
- the nuances of ethical research still elude most Indian researchers due, genuinely, to ignorance,
- the pressure of the pharmaceutical industry to push through research at any cost is overpowering.

Comprehensive texts on the basic principles and guidelines for the ethical conduct of research are readily accessible (3-9) and must be perused by anyone contemplating research.

Research involving children is important for all children but presents unique challenges. Children represent a vulnerable subgroup. It is, therefore, incumbent on parents, researchers and institutions to ensure that their rights are protected and that they are shielded from undue risk. Research with children should be undertaken only if:

(*i*) The same question cannot be answered by research in adults(7).

(*ii*) There is an identifiable prospect of benefit. It must not be done for financial or professional gain(7,10).

(*iii*) The study is well designed and must not merely duplicate earlier works. Scientifically invalid research is also unethical(10).

(*iv*) The investigator is qualified and ensures that the physical, emotional and psychological safety of the child and his family is safeguarded(11).

Three key issues regarding research with children need to be discussed:

1. ***Risk versus benefit***

While considering any research proposal, the risk must be balanced against the likely benefit to the child, or children in general. These risks include not only physical discomfort and inconveniences, but also psychological concerns like fright, separation from parents, and unfamiliar surroundings. With children, another important consideration is the effect on growth and development, a risk that may persist with children for longer. Research in children that does not offer direct benefit has generated substantial controversy. Most guidelines draw a distinction between "therapeutic" (with direct benefit) and "non-therapeutic" (with no direct benefit) research(10,12). It is currently accepted that non-therapeutic research may be permitted if it presents "no greater than minimal risks"(7,10), which may be defined as risks of daily life. Although the assessment of risk is central to ethical review process, there seems to be no coherent criteria to measure risk and benefit. Even the definitions of "minimal risk" and "minor increment over minimal risk" are inconsistent and not uniformly agreed upon.

2. ***Consent***

A child is legally unable to provide

informed consent. Therefore, proxy consent is obtained from the child's parent or guardian. Informed consent must explain the purpose of research, the difference between treatment and research, and the potential risks and benefit. Consent must be voluntary, without coersion or financial inducement. The family must have enough time to think and respond. Refusal to give consent must not jeopardize the child's treatment in any way. It is often recognized that there are problems in asking the parents to consent(13,14). In India particularly, with literacy levels being so low parents may not understand the significance of the risks involved and give consent. Frequently, requests for consent are met with blank, uncomprehending stares and the comment, "You do what you think is right". One study showed that better educated parents were less likely to allow their children to participate in research (15). Equally, if more time was given to parents to reflect on the proposal, they were less likely to consent(16). Interestingly, a court ruling once said that "parents may be free to become martyrs themselves. But it does not follow that they are free to make martyrs of their children"(13). Most current guidelines require.that the, child's assent should also be taken if he is old enough to comprehend; usually over 6-7 years of age. A determined refusal of an older child to participate in the study must be respected despite parental consent (5,7,10).

3. ***Drug trials***

The policy of overprotecting children from drug trials has a flip side: (*a*) There is a relative paucity of good medical research in children. In one review, there were only 249 randomised, controlled trials in children published in one pediatrics journal over a 15 year period(17), and even out of these a large percentage were underpowered. (*b*) Children have not reaped the benefits of pharmaceutical advances to the same extent as adults, rendering them "therapeutic orphans". Many medications, that are widely used in children, are rarely first tested on children(18). Without pediatric studies, labeling cannot include guidance about dosage and side effects. Seventy per cent of the current medications lack sufficient data in children(18). The physician faces a dilemma either not to treat children with a potentially beneficial medication or to treat them empirically with educated guesses about doses, safety and effectiveness(10,18). One study estimated that almost half of all drug prescriptions for children were either "off label" indications or used unlicensed drugs(19). I would reckon that the figure could be much higher in India. Corrective measures have already been initiated and most countries need to follow suit. The US Federal Drug Administration has enacted a "carrot and stick" policy. This mandates that pharmaceutical firms must recruit children in all their drug trials. If children are to be specifically excluded, the firm shall have to present acceptable justification for the same. In return, the FDA shall allow a 6 months additional market exclusivity for data pertaining to the use of tested agents(9).

Industry-sponsored clinical research

We are currently in the midst of an on-slaught of pharmaceutical company sponsored drug trials. While there can be no doubt that this will benefit medical therapeutics generally, we need to ensure that the aftermath of this 'Tsunami wave' leaves us with tangible gains:

(*a*) People who take part in the research trial must benefit by getting the best available treatment when the trial ends(5).

(*b*) Data from all clinical trials is made freely available even if it is unfavorable or

insignificant(20,21). There are in-numerable cases in which commercial interests have suppressed the results of clinical trials. This problem may be circumvented if clinical trials were to be registered centrally with a requirement for periodic reporting of progress and adverse reactions. There are attempts to make this registration a pre-condition to approval by the Institutional Review Boards (IRB). ClinicalTrials.gov is one such database that is a comprehensive public trials registry. There is also a concerted move by the International Committee of Medical Journal Editors (ICMJE) for drug trials to be registered at inception as a condition for later consideration for publication(22).

Research involving humans rests on trust and a general feeling of wanting to be of some use. In return for this trust that a patient places in the research process, the investigators have an obligation to conduct research ethically and to report it honestly(22). Mind-boggling sums of money are at stake in industry sponsored drug research. It has been estimated that a US manufacturer loses over $1 million for each day's delay in gaining approval of a new drug(21). While the primary objective of the industry is to generate profits; the researcher should limit on self to scientific inquiry(21). A marriage of the two agendas is possible. The foremost concern must be the safety and the well-being of the patient.

Where do we go from here?

1. ***Setting priorities***

National bodies must identify priority areas for research and direct funds to these areas. Externally sponsored research must also, by and large, conform to these national priorities. This will minimize exploitation of the vulnerable, socio-economically weaker population and, also, maximize the benefit of research to the community.

2. ***Education***

There is an urgent need to educate the medical fraternity in India in basic research methodology and ethical principles if the level of research has to improve. Thankappan(23) recommended that ethics should be a part of the medical curriculum. The Indian Council of Medical Research (ICMR) must play a more proactive role in this process of education. In addition, external sponsors of research from developed nations have an obligation to contribute to the training of staff in the methods and skills of conducting research(26). The infra-structure and support for quality research needs to be strengthened. The public and the media equally need to be sensitized on the urgent need to include children in clinical research. The fears of parents to let their wards be subjected to research need to be allayed compassionately, and the role of the primary family physician in developing this trust needs to be underscored. Negative media coverage must be proactively balanced with positive stories about the societal benefits of good clinical research(24) Public awareness campaigns would help achieve this goal.

3. ***Improved regulation***

The recently published ICMR guidelines remain recommendatory. They must be made mandatory in law. The recently revised schedule Y of the Drugs and Cosmetics Rule (4) that governs drug trials in India is a welcome step.

4. ***Critical surveillance***

Most institutions in India do not have ethics committees or IRBS. These are mandatory for centers that conduct research, as per the ICMR guidelines. These committees must play the role of the watchdog. Their primary responsibility is to protect the rights of the research subjects as envisaged in the Declaration of Helsinki. They are expected to

monitor ongoing trials, especially for serious adverse events. They must also protect the vulnerable groups, such as children, from profit-driven pharmaceutical companies testing drugs essentially for the developed world(25). Equally, the committees must ensure that consistent ethical standards are followed irrespective of the local settings so that participants from the developing world are safe from exploitation(26).

5. ***Pooling resources***

In a vast and diverse country such as ours, with limited resources, all attempts must be made to improve efficiency while reducing duplication of effort and costs. Multicenter trials will help in recruiting a larger patient load in a shorter span of time. This will also enhance co-operation between institutions. Similarly, clearance of such multicenter trials and their periodic monitoring may be done by a central lRB.

Anurag Krishna,
Senior Consultant,
Department of Pediatric Surgery,
Sir Ganga Ram Hospital ,
New Delhi 110 060, India.
E-mail: anuragkrishna@sgrh.com

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